IN THE CLAIMS

Please cancel claims 35-36 and 38-39 without prejudice.

Please amend claims 34, 37, and 40 as follows:

This listing of claims will replace all prior versions, and listings, of claims in the application. Upon entry of the present amendment, the claims will stand as follows:

1. (Withdrawn) A method for modulating the production of Aß1-40/42 peptide fragments comprising contacting a sample or cell containing a beta-site APP-cleaving enzyme 1 (BACE1) and an amyloid precursor protein (APP) with a BACE1-modulating agent such that production of Aß11-40/42 is modulated.

2. (Withdrawn) The method of claim 1, wherein the modulation is inhibition of A11-40/42 peptide formation.

3. (Withdrawn) The method of claim 1, wherein the contacting is *in vivo*.

4. (Withdrawn) The method of claim 1, wherein the contacting is *in vitro*.

5. (Withdrawn) The method of claim 1, wherein the BACE1-modulating agent is an anti-BACE1 antibody or a BACE1 antisense molecule.

6. (Withdrawn) A method for identifying a compound which inhibits beta-site APP-cleaving enzyme 1 (BACE1) expression or activity comprising:

a) incubating components comprising the compound, BACE1 polynucleotide or polypeptide, and an amyloid precursor protein (APP) under conditions sufficient to allow the components to interact; and

b) measuring the production of a BACE1 specific enzymatic product.

7. (Withdrawn) The method of claim 6, wherein the compound is a peptide or a small molecule inhibitor.

8. (Withdrawn) The method of claim 6, wherein the BACE1 polynucleotide or polypeptide is expressed in a cell.

9. (Withdrawn) The method of claim 6, wherein the BACE1 specific enzymatic product includes a sequence of Aß11-40/42.

10. (Withdrawn) A compound identified by the method of claim 6.

11. (Withdrawn) The compound of claim 10 in a pharmaceutically acceptable carrier.

12. (Withdrawn) A method for diagnosing a subject having or at risk of having an Aß11-40/42 peptide accumulation disease, the method comprising:

measuring the amount of beta-site APP-cleaving enzyme 1 (BACE1) in a biological sample from the subject; and

comparing the amount BACE1 with a normal standard value of BACE1, wherein a difference between the measured amount and the normal sample or standard value provides an indication of the diagnosis of Aß11-40/42.

13. (Withdrawn) The method of claim 12, wherein the biological sample is blood, serum, cerebrospinal fluid or central nervous system (CNS) tissue.

14. (Withdrawn) The method of claim 12, wherein the difference is an increase in BACE1.

15. (Withdrawn) The method of claim 12, wherein the amount BACE1 is measured by detecting the amount of a polynucleotide encoding BACE1.

16. (Withdrawn) The method of claim 15, wherein the polynucleotide is mRNA.

17. (Withdrawn) The method of claim 12, wherein the amount of BACE1 is detected by contacting the sample with an agent that specifically binds to a BACE1 polypeptide.

18. (Withdrawn) The method of claim 17, wherein the agent is an antibody.

19. (Withdrawn) The method of claim 17, wherein the Aß11-40/42 accumulation disease is Alzheimer's disease.

20. (Withdrawn) The method of claim 12 further comprising detecting the level of an APP fragment, wherein an increase in the presence of the fragment is indicative of Alzheimer's disease.

21. (Withdrawn) The method of claim 20, wherein the APP fragment is an Aß1-40, Aß1-42, Aß11-40, or Aß11-42 fragment.

22. (Withdrawn) The method of claim 21, wherein the fragments are detected by contacting the sample with an agent the specifically binds to an Aß1-40, Aß1-42, Aß11-40, or Aß11-42 fragment.

23. (Withdrawn) The method of claim 22, wherein the agent is an antibody.

24. (Withdrawn) A method for diagnosing a subject having or at risk of having Alzheimer's disease, the method comprising:

measuring Aß11-40/42 in a biological sample from the subject; and comparing the amount of Aß11-40/42 with a normal sample or standard value of Aß11-40/42, wherein a difference between the amount in the normal sample or standard value is indicative of a subject having or at risk of having Alzheimer's disease.

25. (Withdrawn) The method of claim 24, wherein the biological sample is cerebrospinal fluid, central nervous system (CNS) tissue, serum or blood.

26. (Withdrawn) The method of claim 24, wherein the difference is an increase in Aß11-40/42 and the increase is indicative of a disposition for Alzheimer's disease.

27. (Withdrawn) The method of claim 24, wherein the difference is a decrease in Aß1`1-40/42.

28. (Withdrawn) The method of claim 24, wherein the amount of Aß11-40/42 is detected by contacting the sample with an agent that specifically binds to Aß11-40/42.

29. (Withdrawn) The method of claim 28, wherein the agent is an antibody.

30. (Withdrawn) A transgenic non-human animal having a transgene disrupting expression of BACE1, chromsomally integrated into the germ cells of the animal, and having a phenotype of reduced A peptide as compared with a wild-type animal.

31. (Withdrawn) The transgenic non-human animal of claim 30, wherein the animal is an avian, bovine, ovine, piscine, murine, or porcine species.

32. (Withdrawn) The transgenic non-human animal of claim 30, wherein the animal is heterozygous or homozygous for the disruption.

33. (Withdrawn) The transgenic non-human animal of claim 30, wherein the transgene comprises a BACE1 antisense polynucleotide.

34. (Presently Amended) A method for identifying an agent that modulates the expression or activity of BACE1, said method comprising:

administering an agent to be tested to [an organism] a wild-type mouse; and

comparing the ~~phenotype~~ BACE1 expression or activity of the ~~organism~~ wild-type mouse contacted with the agent with that of a BACE1-knockout ~~organism~~ mouse not contacted with the agent, whereby ~~a phenotype~~ expression or activity of BACE1 in the wild-type mouse substantially equal to that of the BACE1-knockout ~~organism~~ mouse is indicative of an agent that ~~modulates~~ decreases BACE1 expression or activity.

Claims 35-36 (Cancelled).

37. (Presently Amended) The method of claim 34, wherein the expression of BACE1 in the wild-type mouse is detected by measuring the amount of BACE1 ~~polynucleotide in the organism~~ in the brain tissue of the wild-type mouse.

Claims 38-39 (Cancelled)

40. (Presently Amended) The method of claim 34, wherein the ~~phenotype of the organism is associated with Alzheimer's disease~~ decrease in BACE1 expression or activity

indicates the agent is a suitable candidate for use in treatment of diseases associated with ß-amyloid production in humans.

41. (Withdrawn) A kit useful for the detection of an A11-40/42 accumulation disorder comprising carrier means containing therein one or more containers wherein a first container contains a nucleic acid probe that hybridizes to a nucleic acid sequence BACE1 or an antibody probe specific for BACE1 or Aß11-40/42.

42. (Withdrawn) The kit of claim 41, wherein the probe comprises a detectable label.

43. (Withdrawn) The kit of claim 41, wherein the label is selected from the group consisting of radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

44. (Withdrawn) A method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease in a subject comprising measuring the accumulation of AB11-40/42 peptide fragments in the subject or the level of BACE1 polynucleotide or polypeptide before and after treatment with the compound,

wherein a decrease in accumulation of peptide fragments or a decrease in the level of BACE1 polynucleotide or polypeptide after treatment is indicative of a compound that is effective in treating the disease.

45. (Withdrawn) A substantially purified antibody that specifically binds a beta-site APP-cleaving enzyme 1 (BACE1) polypeptide or an epitopic determinant thereof.

46. (Withdrawn) The antibody of claim 45, which is present in an antiserum.

47. (Withdrawn) The antibody of claim 45, which comprises polyclonal antibodies.

48. (Withdrawn) The antibody of claim 45, which is a monoclonal antibody.

49. (Withdrawn) The antibody of claim 45, wherein the epitopic determinant comprises amino acid residues 46 to 164 of BACE1.

50. (Withdrawn) A method of detecting a beta-site APP-cleaving enzyme 1 (BACE1) polypeptide in a sample, the method comprising contacting the sample with the antibody of claim 45 under conditions that allow specific binding of the antibody to BACE1 or an epitopic determinant thereof, and detecting specific binding of the antibody to a component of the sample.

51. (Withdrawn) The method of claim 50, wherein the sample is a tissue sample, which is obtained from a subject.

52. (Withdrawn) The method of claim 51, wherein the tissue sample is a brain tissue sample.

53. (Withdrawn) The method of claim 51, wherein the subject has or is suspected of having a disorder associated with an accumulation of amyloid plaques.

54. (Withdrawn) The method of claim 53, wherein the disorder is Alzheimer's disease.

55. (Withdrawn) The method of claim 50, wherein the antibody comprises a detectable label, and wherein said detecting specific binding comprises detecting the label.

56. (Withdrawn) The method of claim 50, further comprising contacting the sample with a reagent that specifically binds the antibody, wherein detecting specific binding of the antibody comprises detecting specific binding of the reagent.

Please add new claim 57 as follows:

57. (New) The method of claim 37, wherein the decrease in BACE1 expression is particularly localized to pre-synaptic terminals.